REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Office Action dated April 20, 2007 (U.S. Patent Office Paper No. 20070405). In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 33, 34, 37-41, 43-46, 48-50, 52-54, 55-60; stand for consideration in this application, wherein claims 1-23, 35 – 36, 42, 47, 51 are canceled without prejudice or disclaimer, and claims 33 and 41 are being amended to correct formal errors and to more particularly point out and distinctly claim the subject invention. Claim 24-33 stand withdrawn from consideration in this application. In addition, new claims 55 to 60 are hereby submitted for consideration.

Rejections under 35 U.S.C. § 112, second Paragraph

Claims 53 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly because the claims recite specific fragments of Bet v 1, namely amino acid sequences 1-73 and amino acid sequences 74 – 159, without providing a sequence for Bet v 1 allegedly known to have isoforms according to (Friedly-Hajek et al. Molecular Immunology, 1999, 36:639-645).

Whether isoforms of Bet v 1 do indeed exist is of no material consequence to the scope of this invention in the sense that Bet v 1, the major grass pollen allergen is one of the most common allergens recognized by 95% of tree pollen and food allergic individuals and almost 60-% of them are sensitized exclusively against Bet v 1. (Jarolin et al., 1989, cited as Reference No. 12 in Vrtala et al. (1997) J. Clin. Invest. 99:1673 – 1681). Applicants believe that the amino acid fragments (1-73 and 74 – 159) of any of Friedly-Hajek's isoforms which induce IgE-blocking antibodies and wherein the allergenic activity of the derivative is 50% or less compared to the allergenic activity of naturally occurring Bet v 1 allergen of any isoform falls within the scope of the claims of this invention. Thus, whereas the Examiner is saying

that one of skill in the art may not be apprised of the primary structure of the recited sequences, Applicants believe that properly construed claims of this Application invite fragments 1-73 and 74 – 159 of any known isoform of Friedly-Hajek. For that at least, this ground for rejection should be withdrawn.

Ten years prior to the Friedly-Hajek paper, Breiteneder et al. (1989) The EMBO Journal Vol. 8, No. 7: 1935 – 1938, in collaboration with one of the inventors of the instant invention, isolated and characterized the cDNA coding for Bet v. 1. All references to Bet v. 1 in the Application as well as in Vrtala et al. (1997) J. Clin. Invest. 99:1673 – 1681, cited in the Application as teaching the isolation and purification of recombinant Bet v 1 fragments, F1 and F2, comprising aa 1-73 (MW 8,100 Daltons) and aa 74-159 (MW 9, 461 Daltons) was clearly intended to refer to the said Breitneder Bet v 1 sequence.

However, although Applicants clearly relied upon and clearly intended to incorporate the Vrtala et al. (1997) J. Clin. Invest. 99:1673 – 1681, by reference, to supply the sequence of fragments F1 and F2, they failed to perfect the incorporation by reference as required by 37 CFR 1.57. (See page 8, paragraph 3 of the specification). Because Applicants intended to, but failed to properly incorporate the amino acid sequence of the Fragments F1 (aa 1-73) and F2 (aa 74-159), and because no new matter will be added to the Application in an effort to cure the improper incorporation by reference, leave is asked of the Examiner to allow Applicants to comply with the provisions of 37 CFR 1.57. Applicants understand that this may also involve appending a sequence listing section to the application as well as complying with the sequence listing requirements, including supplying a computer readable form of the sequences.

With the caveat that presenting the primary sequence of the fragments of Bet v.1 referred to in the Application does not limit the Applicability of the inventions to any isoforms of the fragments, Applicants believe that curing the improper incorporation by reference will obviate this ground for rejection.

Another reason why it is imperative to cure the improper incorporation by reference is to erase the discrepancy mentioned on page 13, last paragraph of the Office Action. The Examiner noted that claims 53 and 54 recite aa fragments 1-73 or 74- 159 of Bet v.1, whereas the referenced document, Vrtala et al. (1997) J. Clin. Invest. 99:1673 – 1681, referred to

fragments 1-74 and 75 – 160 respectively. Referring the Examiner to the cDNA sequence shown on Column 2, page 1935 of the Breiteneder e al. (1989) reference, the Examiner will note the ATG (met) initiation codon in position 1. Whereas the Vrtala et al. (1997) document included the initiation codon, the Application omitted it. It is believed that curing the improper incorporation by reference will put paid to this discrepancy and again, leave is asked of the Examiner to do so.

Rejections under 35 U.S.C. § 112, first Paragraph

Claims 33- 34, 37 - 41, 43-46 and 48 - 52 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement, allegedly because the claims while enabling the treatment of birch allergy by administering trimers of Bet v1, aa 1-73, or aa 74-159 of Bet v 1, does not reasonably provide enablement for the treatment or prevention of alder, birch, and hazel allergy by administering general derivatives of the major allergens of alder, birch, and hazel.

The Examiner takes issue with the "prevention" of alder, birch, and hazel allergy stating that the Applicants had not defined prevent and as a term, "prevent' lends itself to two reasonable interpretations. In one interpretation, the Examiner believes that prevent may be construed to mean that "the therapy needs to be initiated prior to reexposure to the allergen such that the development of an allergen specific IgE response never occurs." The other "reasonable interpretation" of "prevention" according to the Examiner is that the therapeutic method is 100% effective in 100% of patients.

Applicants respectively ask the Examiner to withdraw the "100% effectiveness in 100%" of patients since it cannot be a reasonable interpretation of "prevent" when there is no such thing as a therapy that is 100% effective in 100% of patients. Because it is an untenable proposition, it is per se unreasonable. Applicants had not supplied a definition of prevention because it was intended for it to be construed in its plain and ordinary sense within the context of the invention; the invention being concerned with the treatment or prevention of IgE mediated disorders.

Within the context of the invention, there are two at risk people for whom this therapy would have patentable utility. The first at risk group are those who have been pre-sensitized by prior exposure to the wild type allergen and as would be treated by administering the compositions of the present invention. The other at risk group are whose who have not been sensitized by prior expose but whose allergic disorder can be prevented by administering the composition of the present invention in order to block sensitization. For instance, it is well known that children from allergic parents have a much greater risk to develop allergies. Also, those living proximal to the geographic distribution of the trees are also an at risk group whose sensitization can be blocked by treatment with the

compositions of the present invention. Applicants do not see any contextual ambiguity with respect to the use of the word "prevent" and respectfully ask the Examiner to withdraw this ground for rejection.

The Examiner appears to take further issue with the cross-reactivity of the immunotherapeutic agents of the present invention. As far back as 1989, Niederberger et al. (J. Allergy Clin Immunol 1998; 102:579 – 91 (cited as Reference 25 in Mahler et al. (2004) Clin. Exp. Allergy 2004: 34:115-122; observed that recombinant birch pollen allergens contain most of the IgE epitopes present in birch, alder, hornbeam, hazel, and oak pollen. Additionally, Mahler et al. (2004), Id., showed that genetically engineered rBet v 1 derivatives induced IgG1 and IgG2a/b antibodies in mice which cross-reacted with natural Bet v1, as well as Bet v 1- related allergens from alder and hazel and blocked allergic patients' IgE binding to Bet v 1. As now amended, the immunotherapeutic fragments of the present invention are all derived from Bet v 1. and the cross reactivity of those fragments with alder and hazel allergens has long been a settled proposition and thus obviates this basis for rejection.

Regarding the structural identity of the fragments of the present invention, the Examiner recognizes that "there is no art recognized method to distinguish allergic from non-allergic molecules on an a priori structural basis." The Examiner further stated that 'if the identity of the IgE binding epitopes that give rise to the allergic activity of an allergen are precisely known, it is not predictable as to which amino acid positions within an epitope need to be altered by site directed mutagenesis such that IgE binding is abrogated." The Examiner further stated that "even when a precise amino acid within the epitope to be altered is identified, the choice of what that amino acid should be mutated to by site-directed mutagenesis is not predictable since some substituted amino acids reduce IgE binding while others have no effect or unexpectedly increase IgE binding."

These statements by the Examiner implicitly recognize the genius of the present invention which seeks to obviate the difficulties mentioned above by a methodology that is simple, much simpler, effective, and not saddled with undue and untoward experimentation. The intention teaches a relatively straightforward methodology to discriminate molecules with allergenic activity from molecules without allergenic activity based on IgE reactivity, basophil histamine release assays and *in vivo* provocation testing. This methodology can be applied to any isolated fragment of wild type allergens by a skilled artisan without undue experimentation.

The Examiner asserts that until the derivatives administered as part of the claimed method are identified, a skilled artisan would not know how to make and use the derivative. Applicants respectively disagree. Crude allergen extracts have been used in the past as immunotherapeutic agents and are still being used today without one of skill in the art knowing the exact structures of the allergens in the crude extract. Similarly, as pointed out above, the method of this invention obviates the need for structural characterization of allergens and can be practiced without knowing the structure

of the allergen derivative used as immunotherapeutic agent. So long as the fragment or oligomer of Bet v.1, is capable of inducing IgE-blocking antibodies and having allergenic activity which is 50% or less compared to the allergenic activity of Bet v. 1, the method of this invention can be practiced without knowing the primary structure of the agent.

On the basis of the foregoing, the Examiner is respectfully asked to withdraw this ground for rejection.

Rejections under 35 U.S.C. § 112, first Paragraph

Claims 33- 34, 37 - 41, 43-46, 48 - 52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants respectfully disagree.

The foregoing arguments are reiterated as if incorporated herein in their entirety. As at the filing date, Applicants had in their possession a method of treating IgE mediated disorders by periodically administering derivatives of Bet v 1 which so long as the fragment or oligomer of Bet v.1, is capable of inducing IgE-blocking antibodies and having allergenic activity which is 50% or less compared to the allergenic activity of Bet v. 1, the method of this invention can be practiced without knowing the primary structure of the agent. Applicants had in their possession any and all fragments of Bet v 1 having the requisite functionality.

The Examiner is respectfully asked to distinguish inventions where knowing the structure of a biomolecule is essential to its practice and the inventors attempted to define those structures by functions without correlating the structure with the functions, and situations where as here, the invention can be practiced without necessarily knowing the primary structure of the biomolecule. The functionalities mentioned in the instant invention have independent and enabling therapeutic significance and allow the invention as such to be practiced without necessarily identifying the primary sequence of those structures. As such, Applicants respectfully ask the Examiner to withdraw this ground for rejection.

Rejections under 35 U.S.C. § 102(b) and 103(a)

Claims 33- 34, 37 - 40, 43-46, 48, 49, 51, 53, and 54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. 103(a) as obvious over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 33, 34, 37, 46, 48 - 51, 53 - 54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Valenta et al. (WO 99/16467) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 33, 49, and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659) in view of Hem et al.

Claims 33, 38, and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 33, 38-41, and 43 – 45 are rejected under 35 U.S.c. 103(a) as being unpatentable over Valenta et al. (WO 99/16467).

Applicants hereby reiterate the arguments made in the January 29, 2007, Response and Amendments to the previous Office Action and further point and assert that this invention patentably distinguishes from the cited prior art for at least the following enumerated grounds.

1. Vrtala et al. (2000) only uses specifically identified Bet v 1 fragments and thus fails to demonstrate the general principles of the immunotherapeutic utility of different hypoallergens (fragments AND trimer);

2. Vrtala et al. (2000) dealt with only the isolated fragments and not the fragment mix for vaccination;

3. Vrtala et al. (2000) uses mainly complete and incomplete Freunds Adjuvant (CFA, ICFA) which is not allowed for human use and it has been recently demonstrated that hypoallergens given with CFA fail to induce allergen-specific IgG when adsorbed to Alum (See Vrtala et al. (2007) J. Immunol. 179:1730-1739. This also puts paid to the Examiner's argument that it would have been obvious to merely substitute Alum with CFA.

4. The recited dosage levels and the periodicity schedule are not subject to routine optimization. On the contrary, it is experimentally intensive and critical to successful immunotherapy.

In view of the foregoing, Applicants respectfully ask the Examiner to withdraw these grounds for rejection.

Conclusion

In view of the foregoing remarks, Applicants submit that there is no basis for applying the previous rejections to the pending claims and withdrawal of the rejections is respectfully requested. The claims are believed to be in condition for allowance, and Applicant earnestly solicits from the Examiner early notification of allowability.

Should the Examiner have any questions or believe a personal or telephonic interview may be in order, she is invited to contact the undersigned at her earliest convenience.

Respectfully submitted,

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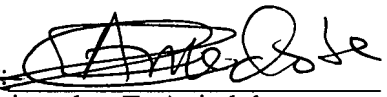
By: 
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